# Is Pneumonectomy After Induction Chemotherapy for Non-small Cell Lung Cancer a Reasonable Procedure? A Multicenter Retrospective Study of 228 Cases

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**Introduction:** Pneumonectomy (PN) after induction chemotherapy (CT) for non-small cell lung cancer is controversial because high-mortality rates are still reported.

**Methods:** This multicenter retrospective study included all patients treated by induction CT then PN between January 1993 and April 2006 in four General and Thoracic Surgery Departments. Postoperative mortality and morbidity and long-term outcomes were studied.

**Results:** The study considered 228 patients. Doublets with cisplatin and vinorelbine or gemcitabine were used in 66% of cases. pTNM stages (World Health Organization, 1997) were 0 (2%), I (16%), II (25%), IIIA (29%), IIIB (16%), and IV (12%). The postoperative morbidity rate was 37% (84 of 228 patients). The independent risk factors identified for postoperative morbidity were chronic obstructive pulmonary disease, more than four cycles of induction CT or an association of cisplatin, and an old cytotoxic molecule, extended PN, and extended anesthesia time. Postoperative mortality rates were 5.3% at 30 days (12 of 228 patients) and 9.2% at 90 days (21 of 228 patients). The independent risk factors identified for operative mortality were chronic obstructive pulmonary disease, manual suture of the stump, and pTNM stage higher than IIIA. The 90-day mortality rates were 10.3% (12 of 117) for right PN and 8.2% (9 of 111) for left PN ($p = 0.65$). The overall survival (OS) rates were 68% at 1 year, 39% at 3 years, and 32% at 5 years.

**Conclusions:** Induction CT was not found to compromise short- or long-term outcomes after PN in non-small cell lung cancer. The right or left PN performed by experienced surgeons after induction CT seems to be a reasonable procedure in case of tumor local extension.

**Key Words:** Non-small cell lung cancer, Induction chemotherapy, Surgery, Pneumonectomy, Chronic obstructive pulmonary disease.

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Despite several phase III studies[1,2] or meta-analyses,[3] induction chemotherapy (CT) failed to show clear benefits in the treatment of resectable non-small cell lung cancer (NSCLC).[4] Nevertheless, induction CT was, and is still, widely used, especially in stage IIIA. Indeed, in stage II, adjuvant CT became recently the new standard recommended by American and French guidelines.[5,6]

Induction CT is generally believed to increase postoperative morbimortality, especially after pneumonectomy (PN). Martin et al.[7] and Doddoli et al.[8] reported unacceptable postoperative mortality rates after induction CT and right PN: 24% and 26%, respectively. The Radiation Therapy Oncology Group 9309 trial reported a 25% mortality rate after concurrent induction CT and radiotherapy (RT) and PN.[9] In the recent American College of Chest Physicians guidelines, full-dose RT is now preferred to PN in stage IIIA after induction RT-CT.[10] PN, especially right PN, after induction CT became the most controversial combination in the treatment of NSCLC and is now contraindicated by many multidisciplinary teams.

However, this new recommendation is based on monocenter retrospective studies that reflect the experience of only one team or on a limited subgroup of randomized trials that included small numbers of patients. Besides, other publications reported more reasonable postoperative mortality rates, 2 to 12%.[11–14]

We conducted a multicenter retrospective study to assess the postoperative morbidity and the 90-day mortality, together with their prognostic factors, and to evaluate the long-term outcomes, in terms of survival and lung function, after induction CT and PN for NSCLC. The asset was the

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inclusion of a large number of patients treated by different oncologic and surgical teams, each with its own procedures and practices.

## PATIENTS AND METHODS

### Patients

All consecutive patients attending four General and Thoracic Surgery Departments in Lyon and Saint-Etienne, France, between January 1, 1993, and April 30, 2006, were included if they had a histologically or cytologically proven NSCLC and were treated by at least one cycle of CT followed by a PN. In accordance with the French legislation, an observational study that does not change the routine management of patients does not need to be declared or submitted to the opinion of a Research Ethics Board.

Although the exact indications could not be collected, preoperative CT was performed during the study period in case of N2 disease suspected on computed tomographic scan or for any reason of doubtful respectability (most cases were suspicions of invasion of great vessels [T4] or small but centrally located tumors). The purpose of CT was to reduce the size of the tumor and facilitate the surgical procedure. Mediastinoscopy was not routinely performed, but complete ipsilateral mediastinal lymphadenectomy was systematically performed.

### Data Collection

During the preoperative period, the following data were recorded: smoking habits, past and current medical comorbidities, hemoglobin and creatinine clearance after the end of induction CT, spirometric parameters, arterial blood gas values, NSCLC characteristics (clinical tumor, node, metastasis, histology, and side), preoperative treatment (CT type, number of cycles and lines, toxicity, delay to surgery, RT, and response).

In the perioperative period, data collection included the surgical procedure (route, method of suture, and method of reinforcement of the bronchial stump), the type of PN (standard or extended), the duration of anesthesia, and the duration of invasive-assisted ventilation.

During the postoperative period, the following data were collected: systematic postoperative monitoring in intensive care unit (ICU) (i.e., monitoring without postoperative complication or specific preoperative risk), the major postoperative complications, the pathological tumor, node, metastasis (pTNM) stage and the quality of the resection, the postoperative treatment (CT and/or RT), the lung function data, the OS, and the progression-free survival (PFS).

### Statistical Analysis

The variables considered as potential prognostic factors for at least one major postoperative complication or for 90-day mortality were first studied by univariate analysis using $\chi^2$ tests (for discrete prognostic factors) or logistic regression (for continuous factors) (Appendix). Because too many variables were explored, of whom some were highly correlated, an initial multivariable model included the classic variables already known as having a prognostic value and found significant in the previous univariate analysis ($p < 0.10$). That first selection of the most representative variables led to a model in which we tested the prognostic impact of additional variables of interest introduced stepwise. After that second selection, a final multiple logistic regression model kept all the variables with a $p$ value less than 0.05 and the clinically relevant variables with a $p$ value between 0.05 and 0.10.

OS and PFS were calculated by the method of Kaplan-Meier. The statistical analyses were performed with S-plus 6.0 software (Insightful).

## RESULTS

### Patient Characteristics

This study included 228 patients whose characteristics are shown in Table 1. The comorbidities were chronic ob-

**TABLE 1.** Characteristics of the 228 Patients and Their Disease

| Characteristics | Values[a] |
|---|---|
| Male | 194 (85) |
| Age | 59 (38–78) |
| Smoking status | |
| Nonsmoker | 15 (7) |
| Current smoker | 102 (45) |
| Former smoker | 99 (43) |
| Hemoglobin[b] (g/dl) | 11.9 (7.7–17.0) |
| Creatinine clearance[b] (ml/min) | 73 (28–150) |
| Preoperative lung function | |
| $FEV_1$ (% predicted) | 85 (47–130) |
| VC (% predicted) | 94 (56–148) |
| $FEV_1$/VC (% predicted) | 72 (44–89) |
| TLC (% predicted) | 99 (56–137) |
| $PaO_2$ (kPa) | 10.9 (6.3–21.2) |
| $PaCO_2$ (kPa) | 4.9 (3.2–7.2) |
| cTNM/pTNM | |
| 0 | —/4 (2) |
| IA | —/8 (4) |
| IB | 11 (5)/28 (12) |
| IIA | 2 (1)/6 (3) |
| IIB | 20 (9)/51 (22) |
| IIIA | 97 (43)/67 (29) |
| IIIB | 71 (31)/36 (16) |
| IV | 22 (10)/28 (12) |
| Unknown | 5 (2)/— |
| Side | |
| Right | 117 (51) |
| Left | 111 (49) |
| Histology | |
| Squamous cell carcinoma | 132 (58) |
| Adenocarcinoma | 67 (29) |
| Large cell carcinoma | 24 (11) |
| Other types | 2 (1) |
| NSCLC unspecified | 3 (1) |

[a] Values are presented with the $n$ (%) or median (min–max) form.
[b] After induction chemotherapy and before surgery.
$FEV_1$, forced expiratory volume in 1 s; VC, vital capacity; TLC, total lung capacity; NSCLC, non-small cell lung cancer; cTNM/pTNM, clinical tumor, node, metastasis/pathological tumor, node, metastasis.

structive pulmonary disease (COPD) in 78 patients (34%), chronic renal failure (creatinine clearance after induction CT <60 mL/min) in 53 (23%), arterial hypertension in 47 (21%), peripheral arterial disease in 29 (13%), another cancer in 30 (13%), body mass index <18 or >30 in 22 (10%), diabetes mellitus in 14 (6%), phlebitis or pulmonary embolism in 14 (6%), coronary disease in 11 (5%), arrhythmia in nine (4%), and chronic heart failure in four (2%) patients. Finally, 29 patients (13%) had three comorbidities or more.

A preoperative mediastinoscopy was performed in 32 patients (14%). Cases of metastasis disease before surgery corresponded to unique metastases mostly operated before thoracic surgery (brain or adrenal gland) or to nodules in another lobe of the same lung. Increased number of metastasis diseases after surgery is explained by unknown nodules found in another lobe by pathologic examination of the resected lung.

## Treatment

Preoperative treatment and surgical procedures are shown in Table 2. Induction CT types were classified into four groups: (i) group 1 ($n = 164$, 72%) had at least one cycle with cisplatin and a last-generation molecule (vinorelbine, gemcitabine, paclitaxel, and docetaxel); (ii) group 2 ($n = 37$, 16%) had at least one cycle with cisplatin but combined only with an "old" cytotoxic agent (mitomycin-C, ifosfamide, vepeside, vindesine, and 5-flurouracil); (iii) group 3 ($n = 25$, 11%) had doublets with carboplatin; and (iv) group 4 ($n = 2$, 1%) had a monotherapy. One percent of the patients received only one induction cycle, 25% received two cycles, 52% received three cycles, 12% received four cycles, and 9% received five cycles or more. Seven percent of the patients received more than one line of CT before surgery.

Twenty-three patients (14%) received preoperative radiation: thoracic radiation ($n = 17$, dose = 56 Gy [40–74 Gy]) or brain radiation ($n = 6$). The time interval between radiation and surgery was unknown.

A partial or a complete treatment response, based on World Health Organization criteria, was achieved in 63% of cases after preoperative treatment. Disease progression was seen in 2% of cases.

Postoperative chest tube drainage was systematically used in the four centers, its median duration was 4 days (range, 1–11). The median posthospital stay was 11 days (range, 2–122).

Adjuvant CT and adjuvant thoracic irradiation (mean dose ± SD: 58 ± 8 Gy) were administered to 18% and 36% of the patients, respectively.

**TABLE 2.** Treatment Modalities

| Treatment | Value |
|---|---|
| Chemotherapy[a] | |
| Group 1 | |
| Cisplatin-vinorelbine | 84 (37%) |
| Cisplatin-gemcitabine | 67 (29%) |
| Cisplatin-vinorelbine-ifosfamide | 9 (4%) |
| Others | 10 (4%) |
| Group 2 | |
| Cisplatin-mitomycin C-ifosfamide | 22 (10%) |
| Cisplatin-vepeside | 8 (4%) |
| Others | 7 (3%) |
| Group 3 | |
| Carboplatin-paclitaxel | 15 (7%) |
| Carboplatin-gemcitabine | 6 (3%) |
| Carboplatin-vinorelbine | 7 (3%) |
| Group 4 | |
| Monotherapy | 2 (1%) |
| Surgical procedure | |
| Intrapericardial route | 89 (39%) |
| Extended pneumonectomy | 70 (31%) |
| Pleural resection | 44 (19%) |
| Parietal resection | 4 (2%) |
| Others | 40 (18%) |
| Suture of the stump | |
| Hand suture only | 41 (18%) |
| Stapling device only | 124 (54%) |
| Both | 61 (27%) |
| Reinforcement of the stump | |
| None | 51 (22%) |
| Biologic paste only | 85 (37%) |
| Pad with or without biologic paste | 89 (39%) |
| Anesthesia | |
| Duration (h) | 2.8 (1.5–7) |
| Systematic postoperative monitoring in ICU | 114 (50%) |
| Duration of postoperative monitoring in ICU (d) | 1 (1–77) |
| Duration of postsurgical invasive ventilation (d) | 0.5 (0.25–23.25) |

[a] Total exceeds 228 because 16 patients received more than one line of induction chemotherapy.
ICU, intensive care unit.

## Short-Term Outcomes

At least one major postoperative morbidity was noted in 37% of the participants. Forty-one patients (18%) had at least one major cardiac or respiratory complication: pneumonia ($n = 17$), acute respiratory failure ($n = 17$), arrhythmia ($n = 16$), pericardial effusion ($n = 3$), pulmonary embolism ($n = 2$), and perioperative cardiac standstill ($n = 1$). Thirty-nine patients (17%) had at least one major surgical complication: hemothorax ($n = 18$), perioperative blood transfusion of more than 2 units ($n = 18$), bronchopleural fistula (BPF, $n = 15$), empyema ($n = 13$), chylothorax ($n = 3$), parietal abscess ($n = 1$), and hypertension of the cavity of PN ($n = 1$). Twenty-four patients (11%) had to be reoperated on for complications: six for BPF with empyema, five for BPF without empyema, four for hemothorax, three for empyema without BPF, two for chylothorax, one for pericarditis with tamponade, one for intestinal obstruction, one for stroke, and one for sepsis. BPF was more frequent when the bronchial stump was closed by hand suture only than when a stapling device was also used (17% versus 4%). The significant factors identified by the univariate analysis were COPD, type of induction CT, hand suture of the stump, extended PN, systematic postoperative monitoring in ICU, pTNM stage >IIIA, low preoperative hemoglobin, increase length of anesthesia, and increase length of inva-

**TABLE 3.** Significant Risk Factors for Major Morbidity Resulting from the Univariate Analysis

| Variables | Rates of Major Morbidities (%) | *p* |
|---|---|---|
| COPD | | <0.05 |
| Yes | 46 | |
| No | 33 | |
| Type of induction CT[a] | | 0.02 |
| Group 1 | 34 | |
| Group 2 | 56 | |
| Group 3 | 28 | |
| Cycles of CT | | 0.055 |
| ≤4 | 36 | |
| >4 | 58 | |
| Suture of the stump | | <0.01 |
| Hand sutured only | 56 | |
| Stapling device only | 28 | |
| Both | 43 | |
| Type of pneumonectomy | | <0.01 |
| Standard | 31 | |
| Extended | 51 | |
| Systematic postoperative monitoring in ICU | | <0.0001 |
| Yes | 53 | |
| No | 24 | |
| pTNM stage | | 0.03 |
| I–IIIA | 33 | |
| IIIB and IV | 48 | |
| Low preoperative hemoglobin | — | 0.03 |
| Extended anesthesia time | — | 0.001 |
| Extended duration of postsurgical invasive ventilation | — | 0.007 |

[a] Group 4 was excluded from the statistical analysis because of its very low number of patients ($n = 2$).

COPD, chronic obstructive pulmonary disease; CT, chemotherapy; ICU, intensive care unit; pTNM, pathological tumor, node, metastasis.

**TABLE 4.** Risk Factors for Major Morbidity Resulting from the Multivariate Analysis

| Variables | Odds Ratio | 95% CI | *p* |
|---|---|---|---|
| COPD[a] | | | |
| No | 1.00 | 0.95–3.86 | 0.07 |
| Yes | 1.91 | | |
| Type of induction CT[b] | | | |
| Group 1 | 1.00 | 1.38–11.68 | 0.01 |
| Group 2 | 4.02 | | |
| Group 3 | 0.34 | 0.10–1.15 | 0.08 |
| Cycles of CT | | | |
| ≤4 | 1.00 | 1.31–13.28 | 0.015 |
| >4 | 4.18 | | |
| Type of pneumonectomy[a] | | | |
| Standard | 1.00 | 1.74–7.80 | 0.001 |
| Extended | 3.68 | | |
| Extended anesthesia time[a] | 1.61 | 1.14–2.26 | 0.006 |
| Extended duration of postsurgical invasive ventilation[a] | 1.01 | 0.94–1.09 | 0.79 |

[a] Variables included in the initial statistical model.

[b] Group 4 was excluded from the statistical analysis because of its very low number of patients ($n = 2$).

COPD, chronic obstructive pulmonary disease; CT, chemotherapy; CI, confidence interval.

**TABLE 5.** Risk Factors for 90-d Mortality Resulting from the Multivariate Analysis

| Variables | Odds Ratio | 95% CI | *p* |
|---|---|---|---|
| COPD | | | |
| Yes | 1.00 | 1.08–8.05 | 0.035 |
| No | 2.95 | | |
| Suture of the stump | | | |
| Hand sutured only | 1.00 | 0.12–1.16 | 0.09 |
| Stapling device only | 0.38 | | |
| Both | 0.22 | 0.05–0.93 | 0.04 |
| pTNM stage | | | |
| I–IIIA | 1.00 | 1.31–9.72 | 0.013 |
| IIIB and IV | 3.56 | | |
| Intrapericardial route | | | |
| No | 1.00 | 0.76–5.87 | 0.15 |
| Yes | 2.11 | | |
| Peripheral arterial disease | | | |
| No | 1.00 | 0.81–8.73 | 0.11 |
| Yes | 2.67 | | |

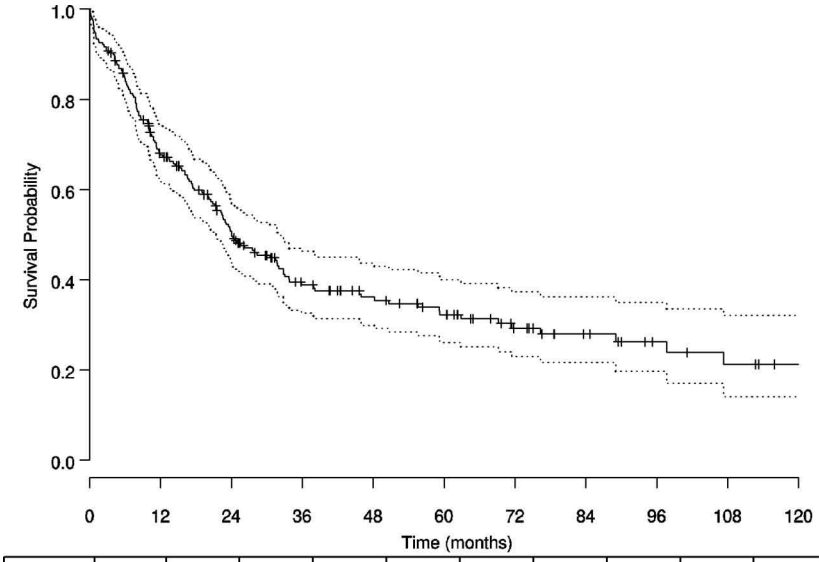
COPD, chronic obstructive pulmonary disease; CI, confidence interval.

sive ventilation after surgical procedure (Table 3). Factors kept in the final multiple logistic regression model are presented in Table 4. Type of induction CT, more than four cycles of induction CT, extended PN, and extended anesthesia time were then statistically significant after multivariate analysis.

The mortality rates at 30 and 90 days were 5.3% (95% confidence interval, CI: 2.7–9.0) and 9.2% (CI: 5.8–13.8), respectively. The causes of the 21 deaths at 90 days were acute respiratory failure unrelated to pneumonia ($n = 6$), pneumonia ($n = 6$), early metastatic relapse ($n = 3$), hemorrhage ($n = 2$), empyema ($n = 1$), acute heart failure ($n = 1$), stroke ($n = 1$), and unknown ($n = 1$). On univariate analysis, the significant risk factors for mortality at 90 days were COPD (16% versus 6% without COPD, $p = 0.03$), peripheral arterial disease (21% versus 8% without peripheral arterial disease), and pTNM stage IIIB or IV (19% versus 6% for pTNM stages I–IIIA). Ninety-day mortality rate was 20% when the stump were hand sutured only versus 7% when a stapling device were used ($p = 0.07$). The mortality rates at 90 days in right and left PN were 10.0% and 8.2%, respectively ($p = 0.65$). On multivariate analysis, the risk factors for mortality at 90 days were COPD, hand suture of the stump, and pTNM stage >IIIA (Table 5).

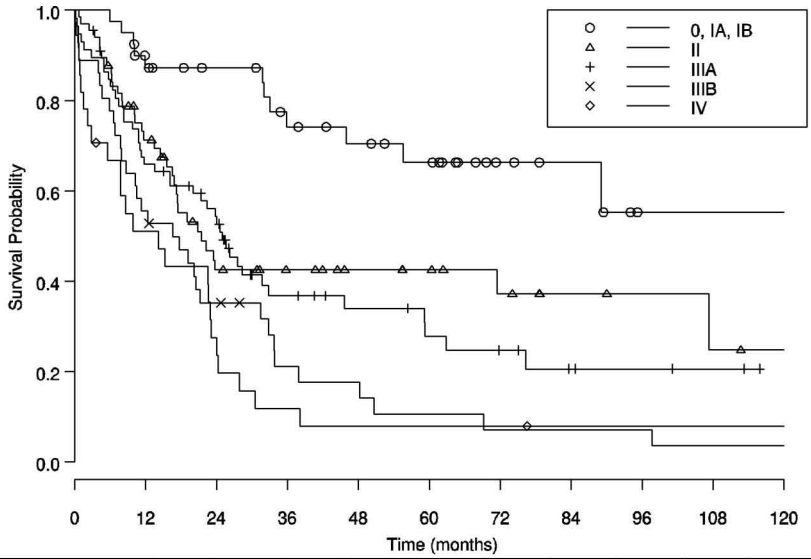
## Long-Term Outcomes

The OS rates at 1, 3, and 5 years were 68%, 39%, and 32%, respectively (Figure 1). The OS rates at 5 years by pTNM stage were 66% for stages 0 to I, 43% for stage II, 28% for stage IIIA, 11% for stage IIIB, and 8% for stage IV




| Month | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients at risk | 228 | 145 | 98 | 63 | 50 | 40 | 26 | 17 | 11 | 8 | 5 |

**FIGURE 1.** Overall survival (Kaplan-Meier method). One, 3, and 5-year survivals were 68%, 39% and 32%, respectively.

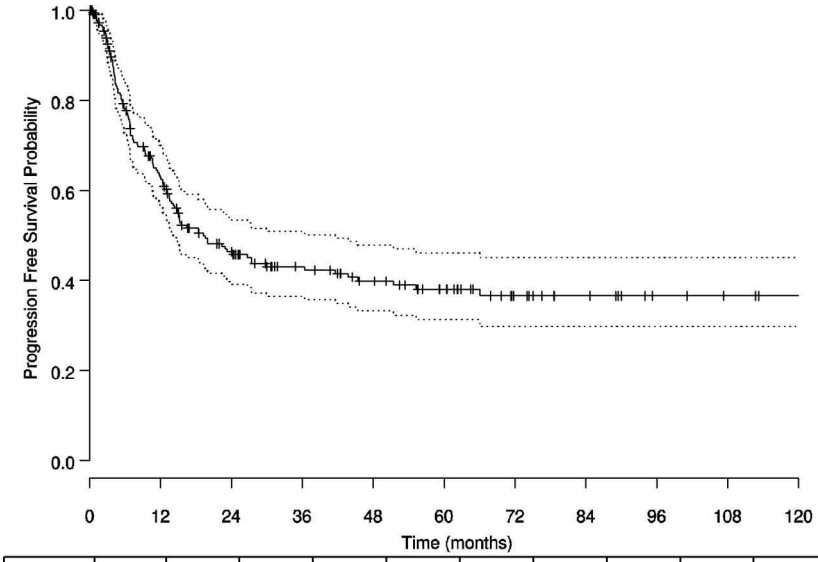



| Month | | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients at risk | p0, pI | 40 | 32 | 28 | 22 | 19 | 16 | 8 | 6 | 2 | 2 | 2 |
| | pII | 57 | 38 | 20 | 16 | 12 | 10 | 7 | 4 | 3 | 2 | 1 |
| | pIIIA | 67 | 42 | 31 | 16 | 12 | 9 | 7 | 4 | 3 | 2 | - |
| | pIIIB | 36 | 20 | 12 | 6 | 5 | 3 | 2 | 2 | 2 | 1 | 1 |
| | pIV | 28 | 13 | 7 | 3 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |

**FIGURE 2.** Overall 5-year survivals by pTNM stage (Kaplan-Meier method). Five-year survivals were 66% for stage 0 to I, 43% for stage II, 28% for stage IIIA, 11% for stage IIIB, and 8% for stage IV.

(Figure 2). Progression-free survival rates were 74% at 1 year, 42% at 3 years, and 38% at 5 years (Figure 3).

Postoperative lung function was available for a subgroup of 138 patients. The median postoperative forced expiratory volume in 1 second ($FEV_1$) was 52% predicted (range, 27–84%), the median postoperative vital capacity (VC) was 58% predicted (range, 30–93%), and the median of the postoperative $FEV_1$/VC ratio was 72% predicted (range, 45–95%). At the end of the follow-up, six of the 228 patients developed a chronic respiratory failure requiring long-time oxygen therapy. One of these six patients required also home mechanical ventilation.




| Month | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients at risk | 228 | 117 | 76 | 56 | 46 | 35 | 21 | 14 | 8 | 6 | 4 |

**FIGURE 3.** Progression-free survival (Kaplan-Meier method). Progression-free survival rates were 74% at 1 year, 42% at 3 years, and 38% at 5 years.

## DISCUSSION

To our knowledge, this work presents the largest series assessing short- and long-term outcomes after induction CT and PN for NSCLC. This multicenter study displayed the outcomes of a wide array of medical and surgical practices and, including consecutive patients, involved a wide range of everyday thoracic oncology cases and avoided selection bias.

However, this study was limited by a retrospective design and inclusion conditions that may have introduced classification bias of some variables. Another limitation of the retrospective design is that the number of patients who could not undergo surgery because of complications of the induction CT or disease progression was difficult to obtain. Because pretherapeutic mediastinoscopy was not systematically performed and positron emission tomography was not available during most of the study period, the cN stage of some patients may have been under- or overestimated before induction CT. No control group was available; thus, the outcomes of our series can only be compared with those of other published series of PN without induction CT. At least, the analysis of the prognostic factors for 90-day mortality was based on a limited number of patients.

In this study, we had to face a high number of potential prognostic variables, which is a potential source of correlations between some of them and a risk of false-positive results, i.e., improper variable selection. Our three-step strategy allowed testing classic variables and other clinically relevant variables stemming from the experience of our team. This strategy had the advantage of being entirely guided by clinical considerations.

Despite the aforementioned caveats, our results led to some interesting conclusions. We found a 37% rate of major morbidity, a 30-day mortality of 5.3%, and a 90-day mortality of 9.2% (8.0% when early metastatic relapse-related deaths are excluded). These unfavorable outcomes are not higher than those reported by most recent series of PN without induction CT: morbidity rates from 39 to 47% and 30-day mortality rates from 6.4 to 9.3%.[15–18] The French recommendation for the 30-day mortality rate after PN is 6% or less[19]; thus, despite a rather wide 95% CI (2.7–9.0), our results are rather encouraging. Moreover, the 5-year OSs by TNM stage compare with those usually reported in NSCLC.[20] Thus, induction CT and PN did not adversely affect the long-term outcomes of our patients. The OS was not obtained to the detriment of the respiratory autonomy: only six patients developed a chronic respiratory failure requiring long-term oxygen therapy. For all these reasons, we believe that induction CT does not compromise short-term and long-term outcomes after PN for NSCLC, even if PN itself remains a major and risky procedure.

Our results suggest caution. First, COPD and pTNM stages >IIIA were found to be independent factors for mortality. COPD has already been identified as a risk factor for morbidity and mortality after PN.[17,21,22] A pTNM stage >IIIA is generally considered as a poor indication for surgery, especially PN, and new diagnostic techniques such as positron emission tomography or endobronchial ultrasound already help clinicians to properly classify patients. In our series, many stage IV diseases were diagnosed after pathologic analysis of the whole lung because a nodule was found in another lobe. In the future TNM classification, these cases will be classified as IIIA when stage $N \leq 1$.[23] Thus, our results suggest that these particular cases should still be considered as poor indications for PN after induction CT. Second, induction CT should be performed with platinum-based doublets with a last-generation molecule for not more than four cycles.[6] In our study, whenever this recommendation was not followed (because it did not exist at that time),

the postoperative morbidity was statistically higher. Third, we have identified three independent factors for unfavorable outcomes during the surgical procedure: extended PN and extended anesthesia time increased postoperative morbidity and hand suture of the bronchial stump increased postoperative mortality. Extended procedures have been already reported to increased morbidity[16] and mortality after PN.[17,21,24] PN after induction CT should be avoided whenever an extended PN seems to be inevitable before surgery (e.g., on radiologic examination). The duration of the surgical procedure in thoracic surgery should be reduced as much as possible.[25–27] This means that PN after induction CT should be performed only by experienced surgeons.[28,29] This opinion will soon be enforced by the French authorities: a minimal rate of thoracic procedures will be required to authorize surgical care of NSCLC in a medical center. In agreement with Darling et al.[18] and with Patel et al.,[22] our study suggests that hand suture of the bronchial stump increases the risk of BPF, a major complication after PN that leads to empyema, respiratory failure, or death.[18,22] In our series, a stapling device was used in 82% of cases, which possibly explains the low number of BPF. It is important to note that, in our series, the method used to suture the stump depended on the surgeon's experience and not, for example, on the extent of the malignant invasion. However, the impact of hand suture of the stump on postoperative mortality has to be considered with caution because the study was not specifically designed to address this question.

The reasons for the lower mortality rate in our retrospective series than in other studies are uncertain but probably linked to several factors: clinical tumor, node, metastasis stage I or II in 15% of the patients, induction CT with platinum and a last-generation molecule doublet in 79% of the patients, a low rate of BPF (7%), and highly experienced centers.

However, with or without induction CT, the intrinsic postoperative morbimortality of PN remains high. Indeed, a 9.2% of mortality rate at 90 days may still seem too heavy, especially versus thoracic radiation in locally advanced stage IIIA NSCLC. Comparing surgery with thoracic RT was not the aim; however, we may note that RT is not consensual in early-stage NSCLC and that surgery, sometimes PN, with CT is proposed to stage II patients. In case of anatomically appropriate early-stage NSCLC, sleeve lobectomy (SL) is an alternative to PN. Yildizeli et al.[30] reported a 30-day mortality rate of 4.1% after SL for NSCLC in a series of 218 patients (none received induction CT). Recently, a small study showed a better postoperative quality of life after SL than after PN.[31] In a meta-analysis including almost 3000 patients, postoperative mortality and long-term survival were lower after SL for NSCLC than after PN (OR = 0.65 [0.42–1.01], $p = 0.05$ and HR = 0.70 [0.62–0.79], respectively).[32] These recent studies suggest that SL should be preferred to PN when anatomically feasible, but they have shown no results about SL after induction CT.

In conclusion, the results of this large multicenter study seem to suggest that induction CT does not compromise short-term and long-term outcomes after PN for NSCLC. When performed by experienced surgeons, right or left PN after induction CT seems to be a reasonable procedure, especially in stage II NSCLC for which thoracic radiation therapy is not consensual. We believe that, in stages II NSCLC or higher, when a PN is required because of local tumor extension, induction CT can be proposed to minimize the size of the tumor. At the least, when SL is not technically or anatomically possible after induction CT, then PN should not be opposed at first.

## APPENDIX

Variables analyzed to determine the risk factors for major postoperative complications: age, sex, withdrawal of tobacco use, quantity of tobacco used, history of ear, nose, and throat carcinoma, COPD, diabetes mellitus, peripheral arterial disease, coronary disease, chronic renal failure, body mass index $<18$ or $>30$, $\geq 3$ comorbidities, preoperative hemoglobin, creatinine clearance, preoperative $PaO_2$, preoperative $PaCO_2$, VC $<75$ (% predicted), number of days between the end of the induction CT and surgery, side of PN, type of induction CT, $>4$ cycles of induction CT, preoperative radiation, tumor response after induction treatment, downstaging N2 after induction treatment, intrapericardial route, type of suture of the stump, extended resection, type of reinforcement of the bronchial stump, histology, pTNM stage, duration of anesthesia, systematic postoperative monitoring in ICU, and length of invasive ventilation after surgical procedure.

Variables analyzed to determine risk factors for 90-day mortality: age, sex, history of COPD, peripheral arterial disease, chronic renal failure, $\geq 3$ comorbidities, preoperative hemoglobin, preoperative PaO2, $FEV_1$, VC, side of PN, type of induction CT, $>4$ cycles of induction CT, preoperative radiation, intrapericardial route, type of suture of the stump, extended resection, type of reinforcement of the bronchial stump, pTNM stage, duration of anesthesia, systematic postoperative monitoring in ICU, and length of invasive ventilation.

All effects of continuous variable were assumed linear after checking nonlinearity using regression splines.

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